Involvement of the Phonatory Functions in Atypical Covid-19 Pneumonia

Original Article

Eman Ezzat Abd El-Wahed[1], Yasser Abd El-Wahab Khalil[2], Asmaa El-Dessouky Rashad[1], Maha Abo Al-Yazeed Al-Kamshishi[3], Hanan Anwar Al-Shorbagy[1]

Department of [1]Phoniatric Unit, ORL, [2]Otolaryngology, Faculty of Medicine, Menoufia University, [3]Phoniatric Unit, ORL, Shebin El-Kom Teaching Hospital Menoufia Egypt.

ABSTRACT

Background: To assess the effect of the COVID-19 pandemic on the voice as many studies reported voice changes in patients with COVID-19.

Objective: This study aimed to sight the involvement of phonatory function in atypical COVID-19 pneumonia. Rather than, enriching our knowledge and medical skills when dealing with that disease in our field.

Patients and Methods: A cross-sectional study was done on one hundred and thirty-five subjects that had COVID-19. The recruited subjects were asked to complete a collective data, scientifically designed questionnaire involving analytical questions about demographic data, COVID-19 general symptoms, comorbidities, otolaryngological symptoms, and dysphonia symptoms. The prevalence of dysphonia, as part of the COVID-19 symptoms, was assessed. The onset, character, and duration were compared between dysphonic and non-dysphonic COVID-19 patients.

Results: A high prevalence (57%) of self-evaluated dysphonia among COVID-19 patients. The current study found no correlation between gender with dysphonia while there is a significant correlation with age. A significant correlation between dysphonia with cough and otolaryngological symptoms was detected. A positive correlation with ventilatory support with or without intubation. Laryngoscopic examination showed that the most affected site was the glottic area by 83.3% where congestion of the vocal fold was the most common abnormality.

Conclusion: Dysphonia may be found in about half of individuals infected with the Coronavirus (COVID-19) pandemic and should be considered as a symptom list of the infection.

Key Words: Covid-19, dysphonia, voice

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Corresponding Author: Maha Abo Al-Yazeed Al-Kamshishi, Department of Phoniatric Unit, ORL Shebin El-Kom Teaching Hospital, Menoufia, Egypt. **Tel.:** +201550023316, **E-mail**: elkamshishimaha@gmail.com

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INTRODUCTION

In December 2019, clusters of atypical pneumonia with unknown etiology emerged in the city of Wuhan in China. In early 2020, the Center for Disease Control in China announced a new corona virus which was officially named severe acute respiratory coronavirus 2 (SARS-COV-2).[1] Since that moment, the new virus has dramatically spread all over the world crossing all country's borders till World Health Organization (WHO) confirmed it as a pandemic disease on March 11, 2020, and health care systems are facing this pandemic and its associated disease which named coronavirus disease 19 (COVID-19).[2] COVID-19 is principally affecting the respiratory system ranging from mild flu-like symptoms to severe respiratory tract infection.[3] The most common symptoms of COVID-19 are fever, cough, myalgia, fatigue, and difficulty of breathing. In addition, there were several ear, nose, and throat (ENT) symptoms; including loss of smell and taste that have been reported as the most common symptoms caused by the virus.[4] SARS-COV-2 virus has upended the world of Otolaryngologists and Phoniatricians as it was observed the occurrence of dysphonia in some COVID-19 patients.[5]

Dysphonia is defined as an alteration in voice quality, pitch, loudness, or vocal effort that may impair communication and/or affect quality of life. Larynx is the box of voice produced in three stage process; respiration, phonation, and resonation. Any alteration in these stage causes dysphonia.[6] COVID-19 virus can cause dysphonia as it interacts with angiotensin-converting enzyme 2 receptor (ACE2) and transmembrane protease serine-2 receptor (TMPRSS2) which is highly expressed in the mucosa of the nose, throat, larynx and vocal folds causing edema, congestion and damage to the mucosa.[7] Another possible cause of dysphonia is a direct invasion of laryngeal innervation due to the neurotrophic and neuroinvasive characteristics of the COVID-19 virus as it affects peripheral and cranial nerves and that was reported in several cases.[8] Dysphonia may also be secondary as a complication of COVID-19 virus infection due to its

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affection on the lungs like causing a lack of respiratory support for phonation, cough, dyspnea, intubation, or fatigue.[9]

The current study found many patients with COVID-19 suffering from dysphonia during the disease, so we planned this study to sight the effect of the COVID-19 pandemic on phonatory function using a collective data scientific designed questionnaire collected electronically or a paper and a pencil format.

PATIENTS AND METHODS:

This study is a cross-sectional study using a structured questionnaire that includes 135 participants that had COVID-19. Participants were selected randomly among those that were positive COVID-19 patients from general society. Participants that were previously had dysphonia before their affection by COVID-19 were excluded. This was determined by questions asked to the participants before accepting to take part in this study and answering the questionnaire. The study protocol was approved by the institutional ethics committee in the Faculty of Medicine, Menoufia University. Participation in the study is completely voluntary. Participants were aware of the study's purpose and their data remained anonymous. This study was passed into 4 steps: I) questionnaire design and construction, II) a pilot study to check any difficulty in understanding the questionnaire questions, III) questionnaire validation, IV) questionnaire application and data collection, and V) statistical analysis.

I. Questionnaire design and construction:

The survey was conducted using a structured questionnaire that is constructed using either a paper and a pencil format or an online questionnaire established on Google Drive and then shared on Facebook and Whats App groups

The questionnaire on voice involvement in COVID-19 patients is composed of 3 sections (Appendix 1), as follows:

Section 1:

It involves questions that help the selection of the participants regarding if he/she had COVID-19 and how he/she know, the investigations made to diagnose COVID-19. If he/she suffers from dysphonia before infection by COVID-19.

Section 2:

It includes the participant’s consent that indicates she/he understood the objectives and benefits of this research well and her/his approval to participate in this study.

Section 3:

It is formed of demographic data like age, gender, COVID-19 disease manifestations as the first symptom appeared, clinical symptoms he/she suffered from like (fever, headache, myalgia, dyspnea, nausea, vomiting, diarrhea, abdominal colic), loss of smell, loss of taste, cough, and its type, criteria, precipitating symptoms if it was intermittent or episodes and how it relieved. The severity of the disease, duration of symptoms, last symptom disappeared and any symptom still suffering from, any concomitant diseases like diabetes mellitus (DM), gastroesophageal reflux disease (GERD), hypertension, and chest asthma were asked. They were asked also if they were transferred to the hospital and if had any respiratory support.

Section 4:

This section is answered only if the participant had dysphonia with COVID-19 symptoms. It aims to collect data on dysphonia and its onset, duration, affection on quality of life, listener's reaction, voice quality, laryngoscopic findings if present, and if still had any voice change till now or recovered completely.

The questionnaire consisted of “YES” or “NO” questions, or choose from multiple choice questions, or answer open-ended questions.

II. Pilot study:

Before applying the questionnaire on voice involvement in COVID-19 to the selected study sample, the questionnaire was applied to 30 participants that had COVID-19 and had the same criteria of selection to ensure that there was no difficulty in understanding the questions and to check the pattern of presentation of the questionnaire items themselves, and their order of presentation. The pilot study group was composed of 30 participants (22 females and 8 males) that had COVID-19. According to the pilot study, some modifications were done like the rearrangement of questions into certain sections, reformulation of some questions to be more clear to the participants, and removal of the repeated questions.

III. Questionnaire validity:

The final form of the questionnaire was validated using content validity by sending the questionnaire on voice involvement in COVID-19 to several professors at the Unit of Phoniatrics, Otorhinolaryngology Department, Faculty of Medicine at Menoufia University. They were asked to answer a questionnaire of six questions about the ability of the questionnaire to deliver information about to what extent of the involvement of voice function in COVID-19 disease and how to deal with it. They were asked to give a score of 1, 2, or 3 signifying weak, good, and excellent.

IV. Questionnaire application and data collection:

The data was collected by either sharing the questionnaire link through different social media platforms (Facebook and WhatsApp) or fulfilled by a paper and a pencil format and the responses to this questionnaire were collected and saved for their analysis.

V. statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 20. Quantitative data were expressed as mean ± standard deviation (SD), the range is expressed in numbers. *P values* of less than 0.05 were considered statistically significant *>0.01* highly significant. Chi-squared test ($\chi 2$) was used to study the association between two qualitative variables. Mann-Whitney test is a test of significance used for comparison between quantitative variables.

RESULTS:

The current study included 135 participants that had COVID-19 disease and didn't have a history of dysphonia before being infected with COVID-19. The data of them were collected. Demographic and COVID-19 manifestations among 135 participants, with the age range of (37.5±13.5) years old, and a male: female ratio of about 2:3. The most prevalent first symptoms were myalgia (60 %). Myalgia, fever, and headache were the high percentage of the general symptoms which are (94.5%), (93.3%) and (89.6%) respectively. Cough was reported by about (77.8 %) of participants and dyspnea was about (18.5%). Loss of smell and loss of taste were (74.1%) and (72.9%) respectively. About (74.4%) had moderate symptoms and the duration of the COVID-19 symptoms ranging between 7 days to 60 days; (25.9%) of them had ventilatory support. Cough and anosmia were the most prevalent symptoms in the last recovered symptoms presenting (29 %) and (27.4%) respectively. (Table 1).

Table 1: Demographic data and Covid-19 symptoms.

Item	Frequency (no=135)	Number (%)
Gender		
- Males	54	40
- Females	81	60
Age in years		
- Mean ± SD	37.5±13.5	
- Min-max	14-70	
First symptom		
- Anosmia	14	10.4
- Eye redness	3	2.2
- Cough	29	21.5
- Dysphonia	2	1.5
- Myalgia	81	60
- Skin rash	6	4.4
Myalgia		
- Yes	128	94.8
- No	7	5.2
Headache		
- Yes	121	89.6
- No	14	10.4
Fever		
- Yes	126	93.3
- No	9	6.7
Rhinorrhea		
- Yes	98	72.6
- No	37	27.4
Cough		
- Yes	105	77.8
- No	30	22.2
Dyspnea		
- Yes	76	56.3
- No	59	43.7
Change of smell		
- Yes	88	65.2
- No	47	34.8
Change of taste		
- Yes	94	69.6
- No	41	30.4

Seventy-seven participants (57 %) reported dysphonia as a COVID-19 symptom while 58 participants (43%) did not report dysphonia during the clinical course of the disease or after it. Three dysphonic participants (3.9%) suffered from dysphonia before other symptoms of the disease appear once while 64 participants (83.1%) had dysphonia during the course of the disease. Ten participants (13%) had dysphonia after the course of the disease. The duration range of dysphonia was (13.6±9.7) days.

The dysphonia affect the quality of life in 49 dysphonic participants (63.6%), about 44 of them (57.1%) described the dysphonia as a moderate degree and 64 (83.1%) had positive listener reactions. The dysphonic participants described the change in their voice as follow; 30 participants (39%) noticed roughness while 24 (31.2%) noticed weakness, 13 (16.9%) noticed voice fatigue and 10 (12.9 %) reported aphonia.

Respiratory tract discomfort was reported by about (94.8%) of dysphoric participants represented by dryness (26%), Globus sensation (31.5%), and sore throat (42.5%). About 30 participants (38.9%) made the laryngoscope examination while 47 (61.1%) didn't make it. The laryngoscope findings were (60%) vocal fold congestion (16.4%) vocal fold immobility mostly unilateral and (6.6%) minimal associated pathological lesions of vocal folds (Figure 1). Sixty-eight dysphonic participants (88.3%) recovered completely without any residual in quality or structure of the vocal folds. While nine dysphonic participants (11.7%) still have not recovered completely. (Table 2).

Table 2: Dysphonia characteristic in covid-19 participants

Item	Frequency (no=135)	Percentage
Dysphonia		
- Yes	77	57
- No	58	43
When did the dysphonia happen		
- Before	3	3.9
- During	64	83.1
- After	10	13
Dysphonia duration in days		
- Mean ± SD	13.6±9.7	
- Min-max	2-90	
Quality of life change		
- Yes	49	63.6
- No	28	36.4
Voice change grade		
- Mild	23	29.9
- Moderate	44	57.1
- Severe	10	13
Listener reacted		
- Yes	64	83.1
- No	13	16.9
Type of voice change		
- Rough	55	71.4
- Weak	24	31.2
- Fatigue	24	31.2
- Aphonia	10	12.9
Respiratory tract discomfort (no=73)		
- Dry	19	26
- Globus sensation	23	31.5
- Sore throat	31	42.5
Recovered dysphonia symptoms		
- Yes	68	88.3
- No	9	11.7
Laryngoscope		
- Yes	30	39
- No	47	61
Videolaryngoscopic findings		
- Congestion of vocal fold	18	60
- unilateral vocal fold paralysis	5	16.4
- MAPLs	2	6.6

There was no significant correlation between dysphonia and gender (*P value = 0.724*). Regarding age, there was a significant correlation between age with dysphonia (*P value = 0.050*). There was a significant correlation between dysphonic participants and otolaryngological symptoms like loss of smell, taste, rhinorrhea, and respiratory tract discomfort. High significant correlation between dysphonia with cough and dyspnea. (Table 3)

Table 3: Correlation between dysphonia and socio-demographic data and otolaryngological symptoms of the recruited participants

Items	Dysphonia (No=77)		No- dysphonia (No=58)		Test of sig. *p-value*
	No	%	No	%	
Gender					
- Male	32	41.6	22	37.9	X^2= 0.181
- Female	45	58.4	36	62.1	*P =0.724 (>0.05)*
Age					
- Mean ± SD	39.4±13.7		34.9±12.8		Mann Whitney U= 1.96
- Min-Max	14-68		15-70		*P =0.050* (≤0.05)*
Change of smell					
- Yes	61	79.2	27	46.6	X^2= 15.6
- No	16	20.8	31	53.4	*P =0.00** (≤0.001)*

Change of taste					
- Yes	62	80.5	32	55.2	X^2= 10.1
- No	15	19.5	26	44.8	*P =0.00** (≤0.001)*
Rhinorrhea					
- Yes	62	78.5	36	64.3	X^2= 23.2
- No	17	21.5	20	35.7	*P =0.00** (≤0.001)*
Respiratory tract discomfort (no=77)					
- Yes	62	80.5	12	20.7	X^2= 13.7
- No	15	19.5	46	79.3	*P =0.00** (≤0.001)*
Cough					
- Yes	74	96.1	31	53.4	X^2= 34.8
- No	3	3.9	27	46.6	*P =0.00** (≤0.001)*
Dyspnea					
- Yes	66	85.7	10	17.2	X^2= 63.04
- No	11	14.3	48	82.2	*P =0.00** (≤0.001)*

P ≤ 0.05 *(Significant), *P ≤0.001* **(highly significant).

A highly significant positive correlation was found between dysphonia and symptom severity. Also, there is a high significance positive correlation between hospital admission and ventilatory support with dysphonia which means that the more the severity of the disease the more the dysphonia expressed. (Table 4).

Table 4: Correlation between dysphonia and COVID-19 severity and respiratory support:

Items	Dysphonia (No=77)		No- dysphonia (No=58)		Test of sig. *p-value*
	No	%	No	%	
Symptoms severity					
- Mild	1	1.3	18	31	X^2= 36.2
- Moderate	49	63.6	38	65.6	*P =0.00** (≤0.001)*
- Severe	27	35.1	2	3.4	
Hospital admission					
- Yes	24	31.2	1	1.7	X^2= 19.01
- No	53	68.8	57	98.3	*P =0.00** (≤0.001)*
Ventilatory support					
- Yes	34	44.2	1	1.7	X^2= 31.02
- No	43	55.8	57	98.3	*P =0.00** (≤0.001)*
High flow nasal					
- Yes	34	100	1	100	------
- No	0	0	0	0	
Invasive support					
- Yes	12	35.3	0	0	X^2= 0.66
- No	22	64.7	1	100	*P =0.737 (>0.05)*

P ≤ 0.05 *(Significant), *P ≤0.001* **(highly significant).

The chronic disease proportion was significantly correlated to the dysphonic group compared to the nondysphonic group (*P value = 0.001*) as dysphonic patients had higher proportions of allergic rhinitis, GERD, and asthma. There was no correlation with diabetes mellitus. (Table 5)

Table 5: Dysphonia in relation to medical history in the recruited patients

Items	Dysphonia (No=77)		No- dysphonia (No=58)		Test of sig. *p-value*
	No	%	No	%	
Chronic diseases					
- Yes	40	51.9	14	24.1	X^2= 10.7
- No	37	48.1	44	75.9	*P =0.001** (≤0.001)*
Allergic rhinitis					
- Yes	25	32.5	7	12.1	X^2= 7.6
- No	52	67.5	51	87.9	*P =0.006* (≤0.05)*
GERD					
- Yes	22	28.6	5	8.6	X^2= 8.2
- No	55	71.4	53	91.4	*P =0.004* (≤0.05)*
DM					
- Yes	8	10.4	5	8.6	X^2= 0.119
- No	69	89.6	53	91.4	*P =0.730 (>0.05)*
Asthma					
- Yes	13	16	2	3.4	X^2= 6.05
- No	64	83.1	56	96.6	*P =0.014* (≤0.05)*

P ≤ 0.05 *(Significant), *P ≤0.001* **(highly significant).

Q1

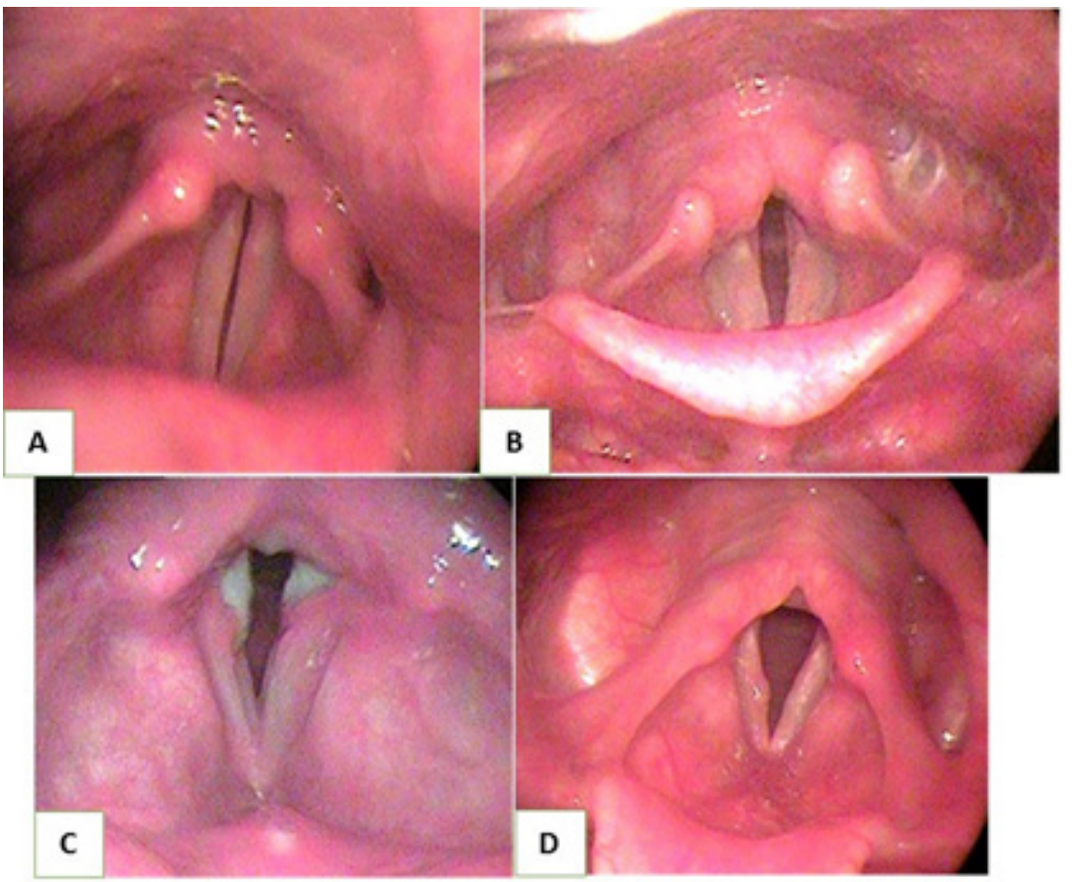

Fig. 1:
A) Immobile right vocal fold (standing in paramedian position) with freely mobile left one.
B) Bilateral vocal folds immobility (standing in paramedian position). Otherwise, they have relatively congested healthy intact covering mucosa
C) Severely edematous and congested both vocal folds with bilateral post-intubation granuloma
D) Right vocal fold MAPL (mainly cyst) secondary to cough with unilateral residual inflammation.

DISCUSSION

The spread of COVID-19 in the world led to the emergence to study the effect of COVID-19 on the phoniatric field and how to deal with this type of patient. There are still updates and questions about its clinical presentation. The general manifestations of COVID-19 are fever, headache, myalgia, cough, dyspnea, anorexia, vomiting, and diarrhea. Also, these manifestations are mainly associated with otolaryngological symptoms like loss of smell, loss of taste, rhinorrhea, and respiratory tract discomfort.

In this regard, many other otolaryngological symptoms could be prevalent in COVID-19. Dysphonia may be one of them as stated in the current study. It highlighted a high prevalence (57%) of self-evaluated dysphonia among those patients. While a previous study by *Lechien et al*. on European cases which was the first study to reveal dysphonia as a relevant symptom in mild-to-moderate COVID-19 patients, showed the prevalence (26.8%).[10] Another study done by *Zayed et al*. stated also a high prevalence of dysphonia was evident in 43.4% of patients.[20]

This study found no correlation of gender with dysphonia and that is consistent with *Cantarella et al*. study.[12] While *Lechien et al*. study found that the female proportion was significantly high in the dysphonic group and explained that by the inflammatory process differences related to gender and to the higher expression of ACE2 in females than males. This leads us not to depend on this theory as a main etiology of laryngeal affection in COVID-19.[11]

There is a significant correlation with age in this study as the younger participants have a lower incidence of COVID-19 infection than older participants due to the expression of ACE2 receptors being less than adults (*Bunyavanich et al*.[19] So, the dysphonia was more expressed in older participants and that is consistent with *Bunyavanich et al*. However, another study done by *Azzam et al* found no correlation of dysphonia with age.[13]

Interestingly, the duration of dysphonia in the described participants was ranging between 2 days to 90 days with (11.7%) of the participant still having dysphonia that exceed three months. This long-term dysphonia is indicative of more severe and longer-lasting impairment in voice production than what is usually seen in viral laryngitis. This interesting observation was consistent with *Cantarella et al*. study. This observation also indicates that the mechanism of dysphonia by the COVID-19 virus differs from other viruses that cause laryngitis and dysphonia. As the SARS-CoV-2 virus affects both upper and lower respiratory tracts we should expect multiple possible causes for the dysphonia with this viral infection.[12]

Dysphonia may be related to the airway inflammatory process involving the larynx and may cause vocal fold edema or inflammation stated also by *Thallapureddy et al*.[22]

Another explanation is the vocal folds have a high expression of angiotensin-converting enzyme 2 (ACE2), which is the COVID-19 receptor so, dysphonia could be caused by direct entry of SARS-CoV-2 into the vocal folds epithelium with consequent infection and damage.[6]

Also, the efficiency of phonation may be affected by respiratory impairment due to lung infection and myalgia. That is supported by the positive association of dysphonia with dyspnea. That is consistent with the results of *Lechien et al*.[10]

The current study showed a significant association between dysphonia with cough and rhinorrhea and that can be explained by the negative effect and irritation of cough to the larynx also, the presence of mucus in the airway due to rhinorrhea with postnasal drip can explain this correlation. That is stated also by a study done by *Azza et al*.[13]

In this regard, another study done by *Lechien et al*., found a positive correlation between dysphonia and cough while they found no correlation between dysphonia and rhinorrhea.[10]

There is a positive correlation between dysphonia and loss of smell and taste and that can be explained and supports the neuroinvasive potential of SARS-CoV-2. A similar finding in *Azza et al*., study supports this finding.[13]

Another positive correlation between ventilatory support with or without intubation and dysphonia seems to be due to the dryness of the mouth and respiratory tract caused by the non-invasive ventilatory support leading to changes in the viscoelastic characteristic of the vocal fold, which contributes to induce dysphonia and worse vocal performance.[14]

As known the risk of laryngeal injury and vocal impairment resulting from intubation however, the study failed to support this finding due to a decrease in the number of participants who were intubated due to most of them died as reported by another study.[15]

The laryngoscopic examination in the current study is performed on only 39% of dysphonic participants, due to the laryngoscopic evaluation being postponed until the patients became non-infectious (negative PCR test). In this regard, this cause is considered a major limitation of this study. It showed that the most affected site was the glottic area by 83.3% and that is consistent with the *Naunheim et al*. investigation which showed that 93.8% of patients

had abnormal findings in the glottis and mainly on closure (50%).[16]

The laryngeal examination showed either vocal folds congestion, unilateral paralysis, MAPLs, or a combination of two or more abnormalities and that is stated also by *Neevel et al*.[21] The congestion of the vocal folds was the most common abnormality in the present study, this is consistent with the study done by *Zhou et al* who indicated that the ACE2 is the receptor of COVID -19 and it is observed a high expression of ACE2 of the vocal folds.[17]

That could be an explanation for the airway inflammatory process involving the larynx resulting in vocal folds edema or inflammation. Five cases had unilateral vocal fold paralysis and this finding was similar to *Saniasiaya et al* result. That may support the neuro-invasive characteristic of COVID-19.[18]

CONCLUSION

Dysphonia was a highly prevalent and long-lasting symptom in COVID-19 patients. In this regard, it has been underestimated to date and could be added to the symptom list of COVID-19. Further research is needed for a long time to shed light on the pathophysiology of voice disorders in COVID-19 patients. Future studies might confirm the relevance of dysphonia as a frequent symptom of COVID-19 disease. Dysphonia involved with COVID-19 is long-lasting but relieved completely with general medication in non-neuroinvasion patients. Little is known about the pathophysiology of those who have lasting neurological defects, thus treatment is currently on trial and based on our knowledge from other populations. Much clinical research is needed for patients with persisting dysphonia to optimize outcomes.

CONFLICT OF INTEREST

There are no conflicts of interest.

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